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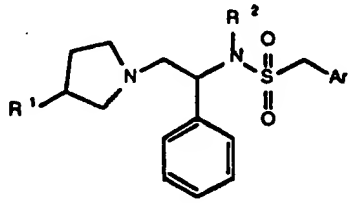

(I)

(57) Abstract

Compounds having chemical formula (I): wherein R^1 is hydrogen, hydroxy, C_1-C_6alkoxy, tri(C_1-C_6alkyl)silyloxy or acyloxy; R^2 is C_1-C_6alkyl; and Ar is optionally substituted aryl. The compounds and their pharmaceutcally acceptable salts have excellent activity as opioid κ-receptor agonists. They are useful for the treatment and prevention of pain, asthma, scabis, psoriasis vulgaris or inflammation, especially pain, in mammalian subjects, e.g., human subjects.

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SULFONAMIDE COMPOUNDS AS OPIOID K-RECEPTOR AGONISTS

Technical Field

This invention relates to novel sulfonamide compounds and their pharmaceutically acceptable salts, and to pharmaceutical compositions for the treatment of pain, asthma, scabies, psoriasis vulgaris, inflammation, in a mammalian subject, especially a human subject.

Background Art

Previously the analgesics, such as morphine, were therapeutically used but their usage was strictly limited because of their side effects such as drug dependency. Thus the analgesics with high usefulness and no drug dependency have been desired. On the other hand, a lot of pharmacological and biochemical studies have been carried out to discover the opioid peptides and opioid receptors. Especially the discovery of the subtype of opioid receptor such as μ, δ, κ at a peripheral nerve in a variety species including human made a beginning towards creating new analgesics. As it is thought that opioid analgesics such as morphine act as a μ-receptor agonist, separating the action based on κ-receptor agonist from the action based on μ-receptor agonist has been tried. Recently κ-selective agonists are reported from the above viewpoint for example, EMD-60400: A. Barber et al., Naunyn-Schmied. Arch. Pharmacol., 345 (Suppl.): Abst 456. Some of them actually have been applied to clinical trial (Med. Res. Rev., 12, 525 (1992)).

Even using selective κ-receptor agonists, when high doses are adopted, side effects such as hallucination, sedation are observed. Therefore the search for excellent analgesics, which have selectively efficacy at peripheral nerve together with high therapeutic coefficient, has been pursued.

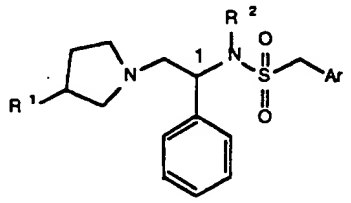
The object of the present invention is to provide the novel sulfonamide compounds with peripheral nerve selective analgesic activity. These sulfonamides show strong κ-receptor agonist activity but weak μ-receptor agonist activity. Another object of the present invention is to provide the pharmaceutical composition containing the novel sulfonamide compounds for pain, asthma, scabies, psoriasis vulgaris, inflammation, the treatment of

congestive heart failure or hypertension, in a mammalian subject, especially a human subject.

In consideration of the above, the inventors made an effort in order to create novel analgesics with high therapeutic coefficient.

Brief Disclosure of the Invention

The present invention provides novel sulfonamide compounds of the formula I:



(I)

and the pharmaceutically acceptable salts thereof,

wherein R^1 is hydrogen, hydroxy, C_1-C_6 alkoxy, tri(C_1-C_6 alkyl)silyloxy or acyloxy;

R^2 is C_1-C_6 alkyl; and

Ar is optionally-sustituted aryl.

The compounds of the formula I show pharmacological activity as κ receptors agonists in mammals, including humans. Therefore they are useful as analgesic agents in mammals, including humans.

Accordingly, this invention also provides pharmaceutical compositions, useful for treating or preventing pain in a mammalian subject, especially a human subject, which comprise a compound of the formula I and a pharmaceutically-acceptable carrier or diluent. Yet further, this invention provides a method for treating or preventing pain in a mammalian subject, especially a human subject, which comprises administering to said mammalian subject an analgesically-effective amount of a compound of the formula I.

Detailed Disclosure of the Invention

In this specification,

the term "alkyl" is used to mean straight or branched hydrocarbon chain radicals including, but not limited to; methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, and the like;

the term "alkoxy" is used to mean -OR (R is alkyl) including, but not limited to,

methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, t-butoxy and the like;

the term "acyl" is used to mean C_2-C_6 alkanoyl, benzoyl or benzoyl having one substitutent selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_1-C_6 fluorinated alkyl (such as fluoromethyl, difluoromethyl or trifluoromethyl), benzyl, pyridylmethyl, halogen (i.e., fluorine, chlorine, bromine or iodine), hydroxy, carboxy, C_2-C_6 alkoxycarbonyl, C_2-C_6 alkanoyl, C_2-C_6 alkanoyloxy, C_2-C_6 alkanoylthio, C_2-C_6 alkanoylamino, carbamoyl, cyano, nitro, mono (C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, amino, C_1-C_6 alkylsulfonylamino, mercapto, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, phenyl and phenoxy;

the term "optionally-substituted aryl" is used to mean aromatic radicals such as phenyl, pyridyl, quinolyl, thienyl, furyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl and pyrazolyl, and their ring-fused derivatives (e.g., benzo-fused derivatives), optionally substituted by at least one substituent selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_1-C_6 fluorinated alkyl (such as fluoromethyl, difluoromethyl or trifluoromethyl), benzyl, pyridylmethyl, halogen (i.e., fluorine, chlorine, bromine or iodine), hydroxy, carboxy, C_2-C_6 alkoxycarbonyl, C_2-C_6 alkanoyl, C_2-C_6 alkanoyloxy, C_2-C_6 alkanoylthio, C_2-C_6 alkanoylamino, carbamoyl, cyano, nitro, mono (C_1-C_6) alkylamino, di(C_1-C_6) alkylamino, amino, C_1-C_6 alkylsulfonylamino, mercapto, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, phenyl, phenoxy and the like.

However, preferred optionally-substituted aryl groups are phenyl, naphthyl, mono-substituted phenyl and mono-substituted naphthyl, wherein the substituent is selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halosubstituted (C_1-C_6) alkyl, halosubstituted (C_1-C_6) alkoxy, C_1-C_6 alkylsulfonyl, nitro, di (C_1-C_6) alkylamino, mono(C_1-C_6) alkylamino monoacylamino, mono (C_1-C_6) alkylsulfonylamino and amino.

A preferred group of compounds of this invention consists of the compounds of formula I, wherein R^1 is hydrogen or hydroxy; R^2 is methyl; and Ar is phenyl, naphthyl or substituted phenyl wherein the substituent is 2-chloro, 2-iodo, 2-nitro, 2-amino, 2-dimethylamino, 2-acetylamino, 2-methansulfonylamino, 3-bromo, 3-methoxy, 3-chloro, 4-chloro, 4-fluoro, 4-methyl, 4-nitro, 4-trifluoromethyl, 4-cyano, 4-methoxycarbonyl, 4-

methansulfonyl, 4-trifluoromethoxy, 2,3-dichloro, 2,4-dichloro, 2,5-dichloro, 2,6-dichloro, 3,4-dichloro, 3,5-dichloro, 3,4-difluoro, 3,5-difluoro or 2,3,6-trichloro.

Preferred individual compounds of the invention are

N-2-(3-hydroxypyrrolidin-1-yl)-1-phenylethyl-N-methyl-(3,4-dichlorophenyl)methanesulfonamide;

N-[2-(3-hydroxypyrrolidin-1-yl)-1-phenylethyl]-N-methyl (2,3-dichlorophenyl)methanesulfonamide;

N-[2-(3-hydroxypyrrolidin-1-yl)-1-phenylethyl]-N-methyl (2,4-dichlorophenyl)methanesulfonamide;

N-[2-(3-hydroxypyrrolidin-1-yl)-1-phenylethyl]-N-methyl (3,4-difluorophenyl)methanesulfonamide;

N-[2-(3-hydroxypyrrolidin-1-yl)-1-phenylethyl]-N-methyl-(4-methylphenyl)methanesulfonamide; and

N-[2-(3-hydroxypyrrolidin-1-yl)-1-phenylethyl]-N-methyl-(4-trifluoromethylphenyl)methanesulfonamide.

The sulfonamide compounds of the present invention can be used in the form of the inorganic salts with acid such as hydrochloric acid, hydrobromic acid, sulfonic acid, nitric acid, phosphoric acid and the like and the organic salts with acid such as acetic acid, formic acid, benzoic acid, oxalic acid, succinic acid, fumaric acid, citric acid, alkylsulfonic acid.

The sulfonamide compounds of this invention possess at least one asymmetric center, and they are capable of occurring in various isomeric forms. The present invention includes all such forms within its scope. The individual isomers can be obtained by methods well known to those skilled in the art, e.g., by fractional crystallization, asymmetric synthesis and the like. Hence, when those skilled in the art use the compounds of this invention, they may choose any desired isomers such as optical isomers or diastereomers, or mixtures thereof.

The following standard methods well known to those skilled in the art can be used in order to obtain the compounds of the present invention.

For example, as shown in Equation 1, they can be synthesized by reacting the

secondary amine (A) with the sulfonyl chloride (B) in an adequate solvent. A base such as triethylamine, pyridine, lutidine or potassium carbonate can be added to the reaction, if desired.

Equation 1

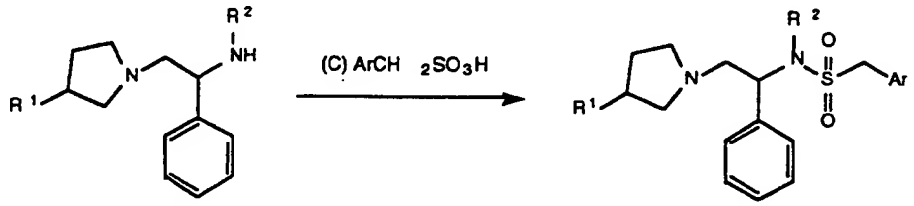
(A) (I)

A solvent which does not react with the reactants or product is preferable. Dichloromethane, tetrahydrofuran (THF), dimethylformamide (DMF), toluene are examples of such a solvent. The base *per se* is also used as a solvent. Temperatures from room temperature to the reflux temperature of the solvent can be used, but the preferable range is from 15 to 100 °C. The progress of the reaction is easily monitored with thin-layer chromatography (TLC). The reaction time is in general from few minutes to several hours. The secondary amine (A) can be synthesized in accordance with the method in the literature (A. Barber et al., Naunyn-Schmled. Arch. Pharm., 345 (Suppl.): Abst 456 and EP 260041), while the sulfonyl chloride (B) is either commercially available or it can be obtained in the similar manner to the method in the following literature. Halogen substitution reaction of sulfonic acid salt: P. D. Bartlett and L. H. Knox, Org. Synth. Col. Vol. V, 196 (1973); reaction of sulfinic acid with halogen: F. Asinger, P. Laue and B. Fell, Chem. Ber., 100, 1696 (1967); reaction of Grignard agent with sulfuryl chloride: S. N. Bhattacharaya, C. Eaborn and D. R. M. Walton, J. Chem. Soc. C, 1265 (1968); halogenation reaction of thiol derivative: I. B. Douglass and T. B. Johnson, J. Amer. Chem. Soc., 60, 1486 (1938) and F. Cortes, Org. Synth. Col. Vol. II, 564 (1943).

On the other hand, as shown in Equation 2, the sulfonamide I can be synthesized by condensation of the secondary amine (A) with the sulfonic acid (C) in an adequate solvent. A well known reagent for peptide synthesis such as 1,3-dicyclohexylcarbodiimide, diethyl azodicarboxylate - triphenylphosphine, diphenylphosphoryl azide (J. Amer. Chem. Soc., 94,

6203 (1972)) can be used as a condensing agent in this reaction. Also in this reaction the activation of sulfonic acid part by 1-hydroxybenzotriazol can be carried out in advance if desired (Chem. Ber., 103, 788, 2024 (1970), J. Amer. Chem. Soc., 93, 6318 (1971) and Helv. Chim. Acta, 56, 717 (1973)).

Equation 2



(A) (I)

A solvent in this reaction which does not react with the reactants or product is preferable. Dichloromethane, THF, DMF and toluene are examples of such a solvent. Temperatures from room temperature to the reflux temperature of the solvent can be used, but the preferable range is from 15 to 100 °C. The progress of the reaction is easily monitored with TLC. The reaction time is in general from few minutes to several hours.

The compounds of this invention can be isolated from the reaction mixture and purified with the well known method to those skilled the in the art, e.g., recrystallization and column chromatographic separation.

The measurement of the binding capacities and affinities *in vitro* of the compounds of the present invention at μ, δ and κ-receptor site are measured by using membrane suspensions from guinea-pig brain sample according to A. L. Regina et al.'s method (J. Recept. Res., 12, 171-180 (1992)). The compounds of the present invention showed the excellent IC_{50} values at κ-receptor. For example, the κ-affinity range of values of the compounds of Examples 1 and 2 was 1.4 nM-1.3 μM and μ-affinity range was more than hundred times weaker than κ-range. The analgesic activity *in vivo* was estimated by S. Hunskaar et al.'s formaline test described in J. Neurosci. Methods, 14, 69-76 (1985). The compounds of the present invention had a good ED_{50} values. For example, the range of values of the compounds in Examples 1 and 2 is 0.1-10 mg/kg (i. p.).

On the other hand, the sedative effect of the compounds of the present invention, which

is thought of as a side effect of opioid analgesic, was measured using the rat rotor rod test (W. T. Kinnard JR. and C. J. Carr, J. Pharmac. exp. Therap., 121, 354 (1957)). Surprisingly, the compounds of the present invention are significantly less active as sedatives than EMD-60400 (A. Barber et al., Naunyn-Schmled. Arch. Pharmacol., 345 (Suppl.): Abst 456).

As mentioned above, the compounds of the present invention have excellent selective κ-agonist activity and in addition reduced the side effects such as sedative effect.

Consequently the novel sulfonamide compounds of formula (I) and their pharmaceutically acceptable salts are useful for treatment of the diseases based on κ-receptor e.g., pain, asthma, scabies, psoriasis vulgaris, inflammation, congestive heart failure or hypertension in a variety of mammalian species including man. In general, for the alleviation of pain in a human subject, these compounds or pharmaceutically acceptable salts may be administered in doses ranging from 0.2 to 500 mg per day, preferably from 1 mg to 300 mg per day, in single or divided doses. Variations will occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out.

The novel sulfonamide compounds or pharmaceutically acceptable salts of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents either orally, parenterally or topically and such administration can be carried out in single or multiple doses. More particularly, the novel therapeutic agents of the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups and the like. Such carriers include solid diluents or fillers, sterile aqueous media, various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds or pharmaceutically acceptable salts of this invention are present in such dosage forms at

concentration levels ranging from 5 to 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch and preferably corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of the sulfonamide compounds or pharmaceutically acceptable salts of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered if necessary, and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

Additionally, it is also possible to administer the compounds or pharmaceutically acceptable salts of the present invention topically to an affected part such as the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

Examples

The present invention is illustrated by the following examples. However, it should be

understood that the invention is not limited to the specific details of these examples. Melting points were taken with a Yanako micro melting point apparatus and uncorrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter in a 10 cm cell. IR spectra were obtained on a Shimadzu IR-470 infrared spectrophotometer. All NMR spectra were measured in $CDCl_3$ by a JEOL NMR spectrometer (JNM-GX270, 270 MHz for ^1H, 67.5 MHz for ^{13}C) unless otherwise indicated and peak positions are expressed in parts per million (ppm) down field from tetramethylsilane. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Example 1

Preparation of N-2-(3-hydroxypyrrolidin-1-yl)-1-phenylethyl-N-methyl-(3,4-dichlorophenyl)methanesulfonamide

(i) 3,4-Dichlorobenzyl bromide

After 3,4-dichlorobenzyl alcohol (5.0 g) and HBr water (16 ml) in dioxane (30 ml) was stirred at 80 °C for 5 hours, the mixture was poured onto saturated sodium chloride solution (150 ml). The solution was extracted three times with each 50 ml of ethyl acetate. The combined organic layer was washed with saturated $NaHCO_3$ and saturated sodium chloride, successively and dried. Concentrating the residue gave the light brown oil (8.44 g, quant.) ^1H NMR δ 7.48 (d, J = 2.2 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.22 (dd, J = 2.2, 8.2 Hz, 1H), 4.41 (s, 2H). IR (film) 1560, 1469, 1439, 1397, 1260, 1225, 1133, 1034, 899, 819, 705, 688, 632 cm^{-1}.

(ii) Sodium 3,4-dichlorobenzylsulfonate

The mixture of 3,4-dichlorobenzyl bromide (8.44 g), sodium sulfite (3.55 g), and tetrabutylammonium bromide (95 mg)in water (25 ml) was stirred at 95 °C for 16 hours. After cooling the precipitate was collected by filtration, washed with acetone, ethyl acetate and ether, successively, and dried to give the title compound (5.0 g, 75 %). IR (film) 1560, 1439, 1397, 1260, 1225, 1133, 1034. ^1H NMR [$(CD_3)_2SO$] δ 7.54 (d, J = 1.9 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.28 (dd, J = 1.9, 8.1 Hz, 1H), 3.74 (s, 2H).

(iii) 3,4-Dichlorobenzylsulfonyl chloride

After the mixture of sodium 3,4-dichlorobenzylsulfonate and phosphorous pentachloride was stirred a 80 °C for 1.5 hours, the resulting oily suspension was poured onto ice-water. Then the mixture was extracted with dichloromethane (260 ml). The extract was washed with saturated $NaHCO_3$ solution and saturated sodium chloride, successively and dried over $MgSO_4$ to give the product (3.74g, 91 %). mp 48-59 C. IR (film) 1471, 1169 cm^{-1}. ^1H NMR δ 7.59 (d, J = 2.2 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.34 (dd, J = 2.2, 8.5 Hz, 1H), 4.80 (s, 2H).

(iv) N-Benzyloxycarbonyl-(S)-phenylglycyl-3-(S)-hydroxypyrrolidine

Diethylphosphonyl cyanide (7.67 g) and N-methylmorpholine (4.57 g) was added dropwise successively to a mixture of 3-(S)-pyrrolidinol (3.28 g) and N-benzyloxycarbonyl-(S)-phenylglycine (10.74 g) in DMF (45 ml) at room temperature. The reaction mixture was stirred for 20 hours. The mixture was poured onto a mixture of water, ether, ethyl acetate and hexane. The separated organic layer was washed with saturated $NaHCO_3$ solution, diluted HCl solution and saturated sodium chloride solution, successively, dried over $MgSO_4$ and concentrated. The resulting crude product was chromatographed on a silica gel column eluting methanol : dichloromethane = 1:50-1:3 to give the product (8.08 g, 61 %). IR (film) 3410, 1721, 1639 cm^{-1}. ^1H NMR δ 7.45-7.25 (m, 10H), 6.31 (t-like, J = 7.7 Hz, 1H), 5.39, 5.35 (two d's, J = 7.7, 8.1 Hz, 1H), 5.15-4.95 (m, 2H), 4.50-4.43 (m, 1H), 3.8-3.0 (m, 4H), 2.0-1.7 (m, 3H).

N-t-butyloxycarbonyl-(S)-phenylglycyl-3-(S)-hydroxypyrrolidine was prepared in a similar manner to the above by using N-t-butyloxycarbonyl-(S)-phenylglycine and can be used for synthesis as a starting material in example 1 (v).

$[\alpha]_D^{25}$ = 121.8° (MeOH, c = 1.00). IR (nujol) 3380, 1705, 1670, 1640 cm^{-1}. ^1H NMR rotamer mixture δ 7.41-7.30 (m, 5H), 5.99 (br d, J = 8.1 Hz, 0.5H), 5.95 (br d, J = 8.1 Hz, 0.5H), 5.37 (br d, J = 8.1 Hz, 0.5 H), 5.33 (br d, J = 8.1 Hz, 0.5H), 4.50-4.38 (m, 1H), 3.80-3.65 (m, 2H), 3.62-3.50 (m, 0.5H), 3.46 (dd, J = 4.4, 13.2 Hz, 0.5H), 3.30-3.22 (m, 0.5H), 3.11 (br d, J = 12.1,. 0.5H), 2.06-1.84 (m, 2H), 1.81 (br s, 1H), 1.41 (s, 4.5H), 1.40 (s, 4.5H).

(v) N-[2-(3-(S)-t-Butyldimethylsilyloxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-

(3,4-dichlorophenyl) methanesulfonamide

The product obtained in (iv)(709 mg) in THF (10 ml) solution was added dropwise to the mixture of $LiAlH_4$ in THF at room temperature with stirring. After starring for three hours at 80 °C, the reaction mixture was cooled down to the room temperature. The reaction was quenched by adding the mixture of $Na_2SO_4 \cdot 10H_2O$. The precipitated salt was filtered off and washed with dichloromethane. The filtrate was concentrated azeotropically with toluene and acetonitrile and the residual crude product has a following IR spectrum. IR (film) 3350, 1674, 1471, 1463, 1252, 1100, 905, 837, 775, 700, 665 cm^{-1}. Then a mixture of imidazole (817 mg), t-butyldimehylsilyl chloride (905 mg) in DMF (5 ml) was added to the crude product and the reaction mixture was stirred at room temperature for three hours. The reaction was quenched by adding a saturated $NaHCO_3$ solution. The mixture was poured onto a mixture of ether, ethyl acetate and hexane. The separated organic layer was washed with saturated sodium chloride solution, dried over $MgSO_4$ and concentrated. The resulting product was adapted the next reaction without further purification. A small amount of the resulting crude product was chromatographed on a silica gel column eluting a mixture of methanol and dichloromethane to give the analytical pure product. IR (film) 3350, 1472, 1439, 1253, 1105, 905, 836, 775, 701 cm^{-1}. ^1H NMR δ 7.4-7.2 (m, 5H), 4.44-4.32 (m, 1H), 3.56 (dd, J = 4.4, 11.0 Hz, 1H), 3.00 (dd, J = 6.4, 9.5 Hz, 1H), 2.82-2.68 (m, 2H), 2.57 (dt, J = 4.8, 8.1 Hz, 1H), 2.38-2.32 (m, 2H), 2.29 (s, 3H), 2.16 (brs, 1H), 2.12-2.00 (m, 1H), 1.72-1.60 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H).

The sulfonyl chloride (623 mg) obtained in the above (iii) and 4-dimethylaminopyridine (586 mg) was added to a solution of the crude product obtained above. After stirring for 16 hours at room temperature, the reaction mixture was partitioned between saturated sodium chloride solution and dichloromethane. The organic layer was dried over MgSO4, concentrated and chromatographed on a silica gel column eluting with ethyl acetate : hexane = 1:40-1:30 to give the analytical pure product (819 mg, 73 %). ^1H NMR δ 7.5-7.2 (m, 8H), 5.32 (dd, J = 2.0, 10.8 Hz, 1H), 4.45-4.35 (m, 1H), 4.40 (AB quartet, J = 13.6 Hz, 2H), 3.35 (t, J = 12.0 Hz, 1H), 3.25-3.15 (m, 1H), 2.7-2.6 (m, 2H), 2.5-

2.35 (m, 4H), 2.25-2.1 (m, 1H), 1.85-1.70 (m, 1H), 0.81 (s, 9H), 0.01, -0.01 (two's, 6H). IR (film) 1470, 1330, 1250, 1140, 1030, 940, 835, 780, 700, 590 cm^{-1}.

(vi) N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(3,4-dichlorophenyl) methanesulfonamide

1M THF solution of tetrabutylammonium fluoride (2.52 ml) was added to a THF solution of the product (704 mg) obtained in (v) (10 ml) at room temperature. After stirring for one hour, the mixture was poured onto a saturated sodium chloride solution (50 ml). The mixture was extracted three times with ethyl acetate. The combined organic layer was dried over $MgSO_4$, concentrated and chromatographed on a silica gel column eluting with methanol : dichloromethane = 1:50- 1:30) to give the titled compound (550 mg, 99 %). IR (KBr) 3450, 1469, 1398, 1325, 1138, 934, 912, 827, 776, 729, 702, 590 cm^{-1}. ^1H NMR δ 7.4-7.3, 7.2-7.14 (m, 8H), 5.20 (dd, J = 4.0, 11.4 Hz, 1H), 4.35 (m, 1H), 4.31, 4.23 (two d's, J = 13.6 Hz, 2H), 3.36-3.24 (m, 2H), 2.84-2.70 (m, 2H), 2.65 (dd, J = 4.0, 12.8 Hz, 1H), 2.50-2.38 (s, 4H), 2.30-2.10 (m, 2H), 1.90-1.70 (m, 1H).

The free base product in (vi) was converted quantitatively to the hydrochloride salt by treating 4M HCl in ethyl acetate solution. IR (KBr) 3450, 1470, 1335, 1160, 930, 780, 710, 590 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_2Cl_2O_3S \cdot HCl \cdot 1/2H_2O$: C, 49.14; H, 5.36; N, 5.73; S, 6.56; Cl, 21.76: Found: C, 49.18; H, 5.62; N, 5.68; S, 6.35; Cl, 21.39.

Example 2

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(4-fluorophenyl)methanesulfonamide

The title compound was synthesized in a manner similar to that of Example 1 from 3,4-dichlorobenzyl bromide and N-[2-(3-(S)-t-butyldimethylsilyloxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine. IR (film) 3450, 1325 cm^{-1}. ^1H NMR δ 7.35-7.15 (m, 7H), 7.02-6.96 (m, 2H), 5.18 (dd, J = 4.4, 11.0 Hz, 1H), 4.35-4.20 (m, 1H), 4.27 (s, 2H), 3.35-3.20 (m, 2H), 2.80-2.72 (m, 2H), 2.67 (dd, J = 4.4, 12.5 Hz, 1H), 2.48 (s, 3H), 2.50-2.14 (m, 3H), 1.85-1.75 (m, 1H).

Example 3

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2-nitrophenyl)methanesulfonamide

The title compound was synthesized in a manner similar to that of Example 1 from (2-nitrophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine. ^{1}H NMR δ 7.98 (dd, J = 1.8, 8.1 Hz, 1H), 7.62-7.48 (m, 3H), 7.37-7.18 (m, 5H), 5.19 (dd, J = 4.4, 11.0 Hz, 1H), 4.94 (d, J = 13.6 Hz, 1H), 4.83 (d, J = 13.9 Hz, 1H), 4.32 (brs, 1H), 3.34-3.25 (m, 2H), 2.80-2.66 (m, 3H), 2.64 (s, 3H), 2.40-2.10 (m, 3H), 1.87-1.75 (m, 1H). IR (film) 3450, 1530, 1355, 1330 cm^{-1}.

Example 4

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2-aminophenyl)methanesulfonamide

The title compound was synthesized by catalytic hydrogenation of N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl-N-methy-(2-nitrophenyl)metanesulfonamide in Example 3 as an intermediate using 10 % palladium carbon in ethanol according to the usal way, followed by deprotecting t-butyldimethylsilyloxy group in a manner similar to that of (vi). IR (film) 3450, 3370, 1325 cm^{-1}. ^{1}H NMR δ 7.38-7.25 (m, 5H), 7.13 (dt, J = 1.5, 7.7 Hz, 1H), 7.01 (d, J = 7.7 Hz, 1H), 6.78-6.72 (m, 2H), 5.34 (dd, J = 3.7, 11.0 Hz, 1H), 4.63 (d, J = 13.9 Hz, 1H), 4.30 (d, J = 13.6 Hz, 1H), 4.35-4.27 (m, 1H), 3.39-3.31 (m, 2H), 2.81 (br d, J = 9.9 Hz, 1H), 2.72-2.64 (m, 2H), 2.54 (s, 3H), 2.30-2.16 (m, 2H), 1.90-1.75 (m, 1H).

Example 5

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl [2-(N',N'-dimethylamino)phenyl]-methanesulfonamide

The title compound was synthesized by dimethylation of N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl-N-methy-(2-aminophenyl)methanesulfonamide in Example 4 as an intermediate according to the A. G. Giumanini's method (Synthesis, 1980, 743), followed by deprotecting t-butyldimethylsilyloxy group in a manner similar to that of (vi). IR (film) 3450, 1325 cm^{-1}.

^{1}H NMR δ 7.63 (br d, J = 6.6 Hz, 1H), 7.39-7.33 (m, 1H), 7.21-7.12 (m, 5H), 6.85-6.82 (m, 2H), 5.05 (dd, J = 4.8, 11.0 Hz, 1H), 4.76 (d, J = 13.9 Hz, 1H), 4.36 (d, J = 13.6 Hz, 1H), 4.25-4.17 (m, 1H), 3.35-3.28 (m, 1H), 3.18 (dd, J = 11.0, 12.2 Hz, 1H), 2.80 (br d, J = 9.2 Hz, 1H), 2.72-2.59 (m, 2H), 2.61 (s, 3H), 2.45 (s, 6H), 2.23-2.06 (m, 3H), 1.85-1.75 (m, 1H).

Example 6

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(3,4-difluorophenyl)methanesulfonamide hydrochloride.

The title compound was synthesized in a manner similar to that of Example 1 from (3,4-difluorophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine. IR (film) 3450, 1330 cm^{-1}. ^{1}H NMR (free base) δ 7.38-7.00 (m, 8H), 5.21 (dd, J = 4.4, 11.4 Hz, 1H), 4.35-4.30 (m, 1H), 4.31 (d, J = 13.9 Hz, 1H), 4.24 (d, J = 13.9 Hz, 1H), 3.33-3.27 (m, 1H), 3.30 (dd, J = 11.4, 13.2 Hz, 1H), 2.81-2.72 (m, 2H), 2.66 (dd, J = 4.4, 13.2 Hz, 1H), 2.49 (s, 3H), 2.40-2.13 (m, 3H), 1.87-1.74 (m, 1H).

Example 7

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(3,5-difluorophenyl)methanesulfonamide hydrochloride

The title compound was synthesized in a manner similar to that of Example 1 from (3,5-difluorophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine. IR (film) 3450, 1320, 1120 cm^{-1}. ^{1}H NMR (free base) δ 7.39-7.29 (m, 3H), 7.23-7.19 (m, 2H), 6.89-6.74 (m, 3H), 5.23 (dd, J =4.0, 11.4 Hz, 1H), 4.38 -4.33 (m, 1H), 4.35 (d, J = 13.6 Hz, 1H), 4.27 (d, J = 13.6Hz, 1H), 3.35-3.25 (m, 1H), 3.31(dd, J = 11.4, 12.8 Hz, 1H), 2.81-2.73 (m, 2H), 2.66 (dd, J = 4.0, 12.8 Hz, 1H), 2.50 (s, 3H), 2.50-2.15 (m, 3H), 1.87-1.75 (m, 1H).

Example 8

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2-acetylaminophenyl)methanesulfonamide hydrochloride

The title compound was synthesized by acetylation of N-[2-(3-(S)-t-

butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl-N-methy-(2-aminophenyl)methanesulfonamide in Example 4 as an intermediate with acetic anhydride in pyridine, followed by deprotecting t-butyldimethylsilyloxy group in a manner similar to that of (vi). IR (Nujol) 3350, 1675,1320, 1130 cm^{-1}. ^1H NMR (free base) 8.78 (br.s, 1H), 7.79 (br.d, J = 7.7Hz, 1H), 7.40-7.29 (m, 4H), 7.26-7.15 (m, 2H), 7.10-6.99 (m, 2H), 5.24 (dd, J =4.4, 11.4 Hz, 1H), 4.45 (d, J = 13.9 Hz, 1H), 4.35-4.30 (m, 1H), 4.33 (d, J = 13.9Hz, 1H), 3.31-3.23 (m, 1H), 3.31(dd, J = 11.4, 12.8 Hz, 1H), 2.78 (d, J = 2.9Hz, 2H), 2.71 (dd, J = 4.4, 12.8 Hz, 1H), 2.55 (s, 3H), 2.35-2.13 (m, 3H), 2.21(s, 3H), 1.85-1.75 (m, 1H).

Example 9

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2-methanesulfonylaminophenyl)-methanesulfonamide hydrochloride

The title compound was synthesized by treatment of N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl-N-methy-(2-aminophenyl)methanesulfonamide in Example 4 as an intermediate with methane sulfonic anhydride, followed by deprotecting t-butyldimethylsilyloxy group in a manner similar to that of (vi). IR (Nujol) 3550, 3250, 1320, 1310, 1140, 1125 cm^{-1}. ^1H NMR (free base) δ 7.51 (dd, J = 1.1, 8.1Hz, 1H), 7.40-7.18 (m, 9H), 5.23 (dd, J =3.7, 11.7 Hz, 1H), 4.76 (d, J = 13.9 Hz, 1H), 4.40-4.32 (m, 1H), 4.30 (d, J = 14.3Hz, 1H), 3.37 (dd, J = 11.7, 12.8Hz, 1H), 3.25-3.17 (m, 1H), 3.10 (s, 3H), 2.83-2.73 (m, 2H), 2.66 (s, 3H), 2.65 (dd, J = 3.7, 12.8Hz, 1H), 2.35-2.11 (m, 3H), 1.88-1.77 (m, 1H).

Example 10

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(4-cyanophenyl)-methanesulfonamide hydrochloride

The title compound was synthesized in a manner similar to that of Example 1 from (4-cyanophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine. IR (film) 3500, 2230, 1330, 1130 cm^{-1}. ^1H NMR (free base) δ 7.60 (d, J = 8.4Hz, 2H), 7.42 (d, J = 8.4Hz, 2H), 7.39-7.31 (m, 3H), 7.20-7.13 (m, 2H), 5.21 (dd, J =4.0, 11.4 Hz, 1H), 4.46 (d, J = 13.5 Hz, 1H), 4.37-4.31 (m, 1H), 4.34

(d, J = 13.5Hz, 1H), 3.32 (dd, J = 11.7, 12.8Hz, 1H), 3.36-3.30 (m, 1H), 2.82 (br.d, J = 9.5Hz, 1H), 2.74 (dd, J = 4.4, 9.9Hz, 1H), 2.66 (dd, J = 4.0, 12.8Hz, 1H), 2.52 (s, 3H), 2.28-2.15 (m, 3H), 1.88-1.75 (m, 1H).

Example 11

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(4-methoxycarbonylphenyl)-methanesulfonamide hydrochloride

The title compound was synthesized in a manner similar to that of Example 1 from (4-methoxycarbonylphenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine. IR (film) 3500, 1720, 1330, 1115 cm^{-1}. ^1H NMR (free base) δ 7.97 (d, J = 8.4Hz, 2H), 7.35 (d, J = 8.4Hz, 2H), 7.32-7.29 (m, 3H), 7.18-7.13 (m, 2H), 5.20 (dd, J =4.4, 11.0 Hz, 1H), 4.40 (d, J = 13.9 Hz, 1H), 4.37-4.28 (m, 1H), 4.34 (d, J = 13.9Hz, 1H), 3.92 (s, 3H), 3.32-3.23 (m, 2H), 2.80-2.71 (m, 2H), 2.67 (dd, J = 4.4, 12.8Hz, 1H), 2.47 (s, 3H), 2.55-2.35 (m, 1H), 2.29-2.12 (m, 2H), 1.87-1.74 (m, 1H).

Example 12

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-phenylmethanesulfonamide hydrochloride

The title compound was synthesized in a manner similar to that of Example 1 from phenylmethanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine. IR (KBr) 3350, 1330, 1155, 1125 cm^{-1}. ^1H NMR (free base) δ 7.35-7.20 (m, 8H), 7.18-7.08 (m, 2H), 5.18 (dd, J = 4.4, 10.8 Hz, 1H), 4.30 (s, 2H), 4.29(brs, 1H), 3.35-3.20 (m, 2H), 2.80-2.68 (m, 3H), 2.48 (s, 3H), 2.30-2.10 (m, 2H), 1.85-1.70 (m, 2H).

Example 13

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(3-bromophenyl)methanesulfonamide hydrochloride

The title compound was synthesized in a manner similar to that of Example 1 from (3-bromophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-

1-yl)-1-(S)-phenylethyl]-N-methylamine. IR (KBr) 3350, 1330, 1155, 1125 cm^{-1}. ^1H NMR (free base) δ 7.55-7.15 (m, 9H), 5.21 (dd, J = 4.4, 11.4 Hz, 1H), 4.35 (brs, 1H), 4.28 (s, 2H), 3.35-3.20 (m, 2H), 2.80-2.72 (m, 2H), 2.68 (dd, J = 4.4, 12.8 Hz, 1H), 2.47 (s, 3H), 2.35-2.10 (m, 3H), 1.87-1.75 (m, 1H).

Example 14

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(4-methylphenyl)methanesulfonamide hydrochloride

The title compound was synthesized in a manner similar to that of Example 1 from (4-methylphenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine. IR (KBr) 3350, 1330, 1155, 1125 cm^{-1}. ^1H NMR (free base) δ 7.38-7.25 (m, 4H), 7.20-7.05 (m, 5H), 5.17 (dd, J = 4.8, 10.6 Hz, 1H), 4.28 (brs, 1H), 4.25 (s, 2H), 3.35-3.15 (m, 2H), 2.80-2.64 (m, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 2.30-2.10 (m, 2H), 1.90-1.70 (m, 1H), 1.65 (brs, 1H).

Example 15

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-2-naphthylmethanesulfonamide hydrochloride

The title compound was synthesized in a manner similar to that of Example 1 from 2-naphthylmethanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine. mp : 235.3-236.1 °C. IR (KBr) 3350, 1340, 1155, 1125 cm^{-1}. ^1H NMR (free base) δ 7.90-7.70 (m, 3H), 7.65-7.42 (m, 4H), 7.30-7.22 (m, 1H), 7.16 (t, J = 7.3 Hz, 2H), 7.04 (d, J = 7.7 Hz, 2H), 5.17 (dd, J = 4.8, 10.6 Hz, 1H), 4.46 (s, 2H), 4.29 (brs, 1H), 3.35-3.14 (m, 2H), 2.82-2.63 (m, 3H), 2.46 (s, 3H), 2.30-2.10 (m, 2H), 1.90-1.55 (m, 2H).

Example 16

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2-iodophenyl)methanesulfonamide hydrochloride

The title compound was synthesized in a manner similar to that of Example 1 from (2-iodophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-

yl)-1-(S)-phenylethyl]-N-methylamine. mp: 191.7-192.5 °C. $[\alpha]_D^{25}$ = +66.0° (MeOH, c=1.0). IR (KBr) 3250, 1330, 1155, 1125 cm^{-1}. ^1H NMR (free base) δ 7.87 (d, J =1.1Hz, 1H), 7.84 (d, J = 1.1Hz, 1H), 7.40-7.23 (m, 4H), 7.18-7.10 (m, 2H), 7.08-7.00 (m, 1H), 5.16 (dd, J = 4.9, 10.8 Hz, 1H), 4.55 (d, J = 14.3Hz, 1H), 4.49 (d, J = 13.9Hz, 1H), 4.27 (brs, 1H), 3.35-3.18 (m, 2H), 2.80-2.65 (m, 3H), 2.72 (s, 3H), 2.25-2.14 (m, 2H), 1.85-1.70 (m, 1H), 1.60 (brs, 1H).

Example 17

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(4-nitrophenyl)methanesulfonamide hydrochloride

The title compound was synthesized in a manner similar to that of Example 1 from (4-nitrophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine. IR (KBr) 3350, 1525, 1350, 1320, 1155, 1125 cm^{-1}. ^1H NMR (free base) δ 8.16 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.37-7.30 (m, 3H), 7.28-7.15 (m, 2H), 5.23 (dd, J = 4.0, 11.4 Hz, 1H), 4.51 (d, J = 13.6 Hz, 1H), 4.39 (d, J = 13.6 Hz, 1H), 4.37 (brs, 1H), 3.40-3.25 (m, 2H), 2.90-2.75 (m, 2H), 2.67 (dd, J = 4.2, 13.0 Hz, 1H), 2.53 (s, 3H), 2.30-2.10 (m, 3H), 1.90-1.75 (m, 1H).

Example 18

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(4-trifluoromethylphenyl)-methanesulfonamide hydrochloride

The title compound was synthesized in a manner similar to that of Example 1 from (4-trifluoromethylphenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-Butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine. IR (KBr) 3350, 1325, 1160, 1125 cm^{-1}. ^1H NMR (free base) δ 7.58 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.35-7.28 (m, 3H), 7.18-7.05 (m, 2H), 5.18 (dd, J = 4.2, 11.2 Hz, 1H), 4.42 (d, J = 13.9 Hz, 1H), 4.34 (d, J = 13.6 Hz, 1H), 4.33 (brs, 1H), 3.39-3.20 (m, 2H), 2.88-2.64 (m, 3H), 2.52 (s, 3H), 2.36 (brs, 1H), 2.30-2.10 (m, 2H), 1.90-1.75 (m, 1H).

Example 19

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(3-

methoxyphenyl)methanesulfonamide hydrochloride

The title compound was synthesized in a manner similar to that of Example 1 from (3-methoxyphenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine. IR (KBr) 3350, 1330, 1155, 1125 cm^{-1}. ^1H NMR (free base) δ 7.38-7.20 (m, 4H), 7.18-7.10 (m, 2H), 6.92-6.80 (m, 3H), 5.19 (dd, J = 4.8, 11.0 Hz, 1H), 4.30 (brs, 1H), 4.28 (s, 2H), 3.75 (s, 3H), 3.35-3.20 (m, 2H), 2.85-2.65 (m, 3H), 2.49 (s, 3H), 2.30-2.10 (m, 2H), 1.90-1.60 (m, 2H).

Example 20

Preparation of N-[2-(3-(S)-(t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2-chlorophenyl)methanesulfonamide

The title compound was synthesized in a manner similar to that of Example 1 from (2-chlorophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine.

(2-Chlorophenyl)methanesulfonyl chloride

IR (film) 1375, 1171, 1055, 1038 cm^{-1}. ^1H NMR δ 7.63-7.25 (m, 4H), 5.12 (s, 2H).

N-[2-(3-(S)-(t-Butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2-chlorophenyl)methanesulfonamide

IR (KBr) 1330, 1259, 1148, 1031 cm^{-1}. ^1H NMR δ 7.60-7.55 (m, 1H), 7.46-7.28 (m, 8H), 5.33 (dd, J = 4.4, 10.8 Hz, 1H), 4.83 (d, J = 13.9 Hz, 1H), 4.56 (d, J = 13.9 Hz, 1H), 4.44-4.36 (m, 1H), 3.28 (dd, J = 10.6, 12.8 Hz, 1H), 3.16-3.02 (m, 2H), 2.80 (dd, J = 4.4, 12.8 Hz, 1H), 2.71 (s, 3H), 2.60-2.50 (m, 2H), 2.23-2.08 (m, 1H), 1.84-1.70 (m, 1H), 0.83 (s, 9H), 0.02, 0.00 (two's, 6H).

Example 21

Preparation of N-[2-(3-(S)-(t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(3-chlorophenyl)methanesulfonamide

The title compound was synthesized in a manner similar to that of Example 1 from (3-chlorophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine.

(3-Chlorophenyl)methanesulfonyl chloride

IR (film) 1374, 1168, 1035 cm^{-1}. ^1H NMR δ 7.50-7.26 (m, 4H), 4.83 (s, 2H).

N-[2-(3-(S)-(t-Butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(3-chlorophenyl)methanesulfonamide

IR (film) 1472, 1329, 1254, 1139, 1035 cm^{-1}. ^1H NMR δ 7.43-7.25 (m, 9H), 5.34 (dd, J = 3.7, 11.4 Hz, 1H), 4.47 (AB quartet, J = 13.6 Hz, 2H), 4.44-4.35 (m, 1H), 3.33 (dd, J = 11.7, 12.5 Hz, 1H), 3.23-3.12 (m, 1H), 2.98 (dd, J = 5.7, 9.9 Hz, 1H), 2.72-2.60 (m, 2H), 2.53-2.42 (m, 1H), 2.38 (s, 3H), 2.23-2.10 (m, 1H), 1.84-1.70 (m, 1H), 0.80 (s, 9H), -0.01, -0.02 (two's, 6H).

Example 22

Preparation of N-[2-(3-(S)-(t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(4-chlorophenyl)methanesulfonamide

The title compound was synthesized in a manner similar to that of Example 1 from (4-chlorophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine.

(4-Chlorophenyl)methanesulfonyl chloride

IR (film) 1490,1359, 1151 cm^{-1}. ^1H NMR δ 7.42 (brs, 4H), 4.83 (s, 2H).

N-[2-(3-(S)-(t-Butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(4-chlorophenyl)methanesulfonamide

IR (KBr) 1325, 1137, 1030 cm^{-1}. ^1H NMR δ 7.4-7.3 (m, 9H), 5.35 (dd, J = 3.1, 11.4 Hz, 1H), 4.50 (AB quartet, J = 13.6 Hz, 2H), 4.45-4.35 (m, 1H), 3.38 (t, J = 12.5 Hz, 1H), 3.28-3.18 (m, 1H), 2.94 (dd, J = 5.5, 9.9 Hz, 1H), 2.6 (dt, J = 3.1, 12.9 Hz, 2H), 2.50-2.37 (m, 4H), 2.25-2.10 (m, 1H), 1.85-1.70 (m, 1H), 0.80 (s, 9H), -0.01 (s, 6H).

Example 23

Preparation of N-[2-(3-(S)-(t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2,3-dichlorophenyl)methanesulfonamide

The title compound was synthesized in a manner similar to that of Example 1 from (2,3-dichlorophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-

butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine.

(2,3-Dichlorophenyl)methanesulfonyl chloride

IR (film) 1428, 1372, 1167, 1035 cm^{-1}. ^1H NMR δ 7.60 (dd, J = 1.5, 7.7 Hz, 1H), 7.52 (dd, J = 1.5, 7.7 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 5.16 (s, 2H).

N-[2-(3-(S)-(t-Butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2,3-dichlorophenyl)methanesulfonamide

IR (film) 1426, 1330, 1254, 1140, 1035 cm^{-1}. ^1H NMR δ 7.46 (dd, J = 1.6, 7.7 Hz, 1H), 7.43 (dd, J = 1.6, 7.7 Hz, 1H), 7.36-7.28 (m, 5H), 7.19 (t, J = 7.7 Hz, 1H), 5.30 (dd, J = 4.0, 11.0 Hz, 1H), 4.87 (d, J = 13.6 Hz, 1H), 4.58 (d, J = 13.6 Hz, 1H), 4.40-4.32 (m, 1H), 3.35 (dd, J = 11.0, 13.2 Hz, 1H), 3.10 (q like, J = 6.2 Hz, 1H), 2.99 (dd, J = 5.5, 9.5 Hz, 1H), 2.74 (dd, J = 4.0, 13.2 Hz, 1H), 2.68 (s, 3H), 2.54 (dd, J = 1.6, 9.5 Hz, 1H), 2.50-2.40 (m, 1H), 2.18 -2.03 (m, 1H), 1.80-1.67 (m, 2H), 0.77 (s, 9H), -0.03, -0.05 (two's, 6H).

Example 24

Preparation of N-[2-(3-(S)-(t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2,4-dichlorophenyl)methanesulfonamide

The title compound was synthesized in a manner similar to that of Example 1 from (2,4-dichlorophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine.

(2,4-Dichlorophenyl)methanesulfonyl chloride

IR (film) 1475, 1378, 1170 cm^{-1}. ^1H NMR δ 7.57-7.52 (m, 2H), 7.44-7.38 (m, 1H), 5.07 (s, 2H).

N-[2-(3-(S)-(t-Butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2,4-dichlorophenyl)methanesulfonamide

IR (film) 1473, 1331, 1249, 1140, 1035 cm^{-1}. ^1H NMR δ 7.48 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 2.2 Hz, 1H), 7.36-7.28 (m, 5H), 7.24 (dd, J = 2.2, 8.4 Hz, 1H), 5.29 (dd, J = 4.0, 11.4 Hz, 1H), 4.77 (d, J = 13.8 Hz, 1H), 4.48 (d, J = 13.8 Hz, 1H), 4.40-4.32 (m, 1H), 3.29 (dd, J = 11.4, 12.8 Hz, 1H), 3.10 (q like, J = 6.6 Hz, 1H), 2.97 (dd, J = 5.5, 9.5 Hz, 1H), 2.72 (dd, J = 4.0, 12.8 Hz, 1H), 2.66 (s, 3H), 2.56 (dd, J = 1.6, 9.5 Hz, 1H), 2.50-2.40 (m, 1H), 2.20-

2.02 (m, 1H), 1.82-1.68 (m, 2H), 0.79 (s, 9H), -0.02, -0.04 (two's, 6H).

Example 25

Preparation of N-[2-(3-(S)-(t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2,6-dichlorophenyl)methanesulfonamide

The title compound was synthesized in a manner similar to that of Example 1 from (2,6-dichlorophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine.

(2,6-Dichlorophenyl)methanesulfonyl chloride

IR (film) 1439, 1378, 1213, 1173, 1131, 1094 cm^{-1}. ^1H NMR δ 7.46 (d, J = 9.2 Hz, 1H), 7.45 (d, J = 6.6 Hz, 1H), 7.36 (dd, J = 6.6, 9.2 Hz, 1H), 5.44 (s, 2H).

N-[2-(3-(S)-(t-Butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2,6-dichlorophenyl)methanesulfonamide

IR (KBr) 1436, 1331, 1139, 1038 cm^{-1}. ^1H NMR δ 7.42-7.28 (m, 7H), 7.19 (dd, J = 7.3, 8.8 Hz, 1H), 5.35 (dd, J = 3.7, 11.4 Hz, 1H), 4.98 (d, J = 14.1 Hz, 1H), 4.74 (d, J = 14.1 Hz, 1H), 4.43-4.33 (m, 1H), 3.35 (dd, J = 11.4, 12.8 Hz, 1H), 3.15 (q like, J = 6.6 Hz, 1H), 3.07 (dd, J = 5.9, 9.5 Hz, 1H), 2.78 (s, 3H), 2.74 (dd, J = 3.7, 12.8 Hz, 1H), 2.58-2.43 (m, 2H), 2.20-2.04 (m, 1H), 1.86-1.76 (m, 2H), 0.78 (s, 9H), -0.01, -0.04 (two's, 6H).

Example 26

Preparation of N-[2-(3-(S)-(t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(3,5-dichlorophenyl)methanesulfonamide

The title compound was synthesized in a manner similar to that of Example 1 from (3,5-dichlorophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine.

(3,5-Dichlorophenyl)methanesulfonyl chloride

IR (KBr) 1365, 1174 cm^{-1}. ^1H NMR δ 7.49 (t, J = 1.8 Hz, 1H), 7.39 (d, J = 1.8 Hz, 2H), 4.79 (s, 2H).

N-[2-(3-(S)-(t-Butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(3,5-dichlorophenyl)methanesulfonamide

IR (KBr) 1323, 1136, 1033 cm^{-1}. ^1H NMR δ 7.36-7.26 (m, 8H), 5.31 (dd, J = 3.7, 11.0 Hz, 1H), 4.52 (d, J = 13.6 Hz, 1H), 4.38 (d, J = 13.6 Hz, 1H), 4.44-4.34 (m, 1H), 3.30 (dd, J = 11.0, 12.8 Hz, 1H), 3.22-3.10 (m, 1H), 2.70-2.60 (m, 2H), 2.48-2.36 (m, 1H), 2.41 (s, 3H), 2.22-2.08 (m, 1H), 1.84-1.70 (m, 2H), 0.81 (s, 9H), 0.00, -0.02 (two's, 6H).

Example 27

Preparation of N-[2-(3-(S)-(t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2,5-dichlorophenyl)-methanesulfonamide

The title compound was synthesized in a manner similar to that of Example 1 from (2,5-dichlorophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine.

(2,5-Dichlorophenyl)methanesulfonyl chloride

IR (KBr) 1472, 1362, 1170, 1150 cm^{-1}. ^1H NMR δ 7.60 (d, J = 2.2 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.40 (dd, J = 2.2, 8.8 Hz, 1H), 5.06 (s, 2H).

N-[2-(3-(S)-(t-Butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2,5-dichlorophenyl)methanesulfonamide

IR (KBr) 1471, 1332, 1253, 1140 cm^{-1}. ^1H NMR δ 7.59 (d, J = 2.2 Hz, 1H), 7.38-7.29 (m, 6H), 7.23 (dd, J = 2.2, 8.4 Hz, 1H), 5.34 (dd, J = 3.7, 11.4 Hz, 1H), 4.82 (d, J = 13.5 Hz, 1H), 4.53 (d, J = 13.5 Hz, 1H), 4.42-4.53 (m, 1H), 3.33 (dd, J = 11.4, 13.0 Hz, 1H), 3.17 (q like, J = 6.0 Hz, 1H), 2.97 (dd, J = 4.0, 9.5 Hz, 1H), 2.71 (dd, J = 3.7, 13.0 Hz, 1H), 2.64-2.56 (m, 4H), 2.50-2.40 (m, 1H), 2.21-2.06 (m, 1H), 1.82-1.68 (m, 2H), 0.78 (s, 9H), -0.03, -0.04 (two's, 6H).

Example 28

Preparation of N-[2-(3-(S)-(t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2,3,6-trichlorophenyl)-methanesulfonamide

The title compound was synthesized in a manner similar to Example 1 from (2,3,6-trichlorophenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine.

(2,3,6-Trichlorophenyl)methanesulfonyl chloride

IR (film) 1440, 1382, 1189 cm^{-1}. ^1H NMR δ 7.54 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 5.47 (s, 2H).

N-[2-(3-(S)-(t-Butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(2,3,6-trichlorophenyl)methanesulfonamide

IR (KBr) 1435, 1328, 1140, 1039 cm^{-1}. ^1H NMR δ 7.39 (d, J = 8.8 Hz, 1H), 7.38-7.34 (m, 5H), 7.30 (d, J = 8.8 Hz, 1H), 5.35 (dd, J = 3.7, 11.4 Hz, 1H), 5.05 (d, J = 14.3 Hz, 1H), 4.78 (d, J = 14.3 Hz, 1H), 4.44-4.36 (m, 1H), 3.35 (dd, J = 11.4, 13.2 Hz, 1H), 3.19 (q like, J = 6.6 Hz, 1H), 3.02 (dd, J = 5.5, 9.5 Hz, 1H), 2.79 (s, 3H), 2.73 (dd, J = 3.7, 13.2 Hz, 1H), 2.58 (dd, J = 1.6, 9.5 Hz, 1H), 2.50-2.40 (m, 1H), 2.20-2.04 (m, 1H), 1.86-1.74 (m, 2H), 0.77 (s, 9H), -0.02, -0.04 (two's, 6H).

Example 29

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(4-methanesulfonylphenyl)-methanesulfonamide

The title compound was synthesized in a manner similar to that of Example 1 from (4-methanesulfonylphenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine.

N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(4-methanesulfonylphenyl)methanesulfonamide

IR (KBr) 3320, 1330, 1300, 1150 cm^{-1}. ^1H NMR δ 7.90 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.40-7.18 (m, 5H), 5.24 (dd, J = 4.2, 11.4 Hz, 1H), 4.53 (d, J = 13.6 Hz, 1H), 4.36 (d, J = 13.6 Hz, 1H), 4.40-4.30 (m, 1H), 3.40-3.28 (m, 2H), 3.06 (s, 3H), 2.86-2.75 (m, 2H), 2.70 (dd, J = 4.2, 13.0 Hz, 1H), 2.56 (s, 3H), 2.35-2.15 (m, 2H), 1.90-1.55 (m, 2H).

Example 30

Preparation of N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(4-trifluoromethoxyphenyl)-methanesulfonamide

The title compound was synthesized in a manner similar to that of Example 1 from (4-methanesulfonylphenyl)methanesulfonyl chloride and N-[2-(3-(S)-t-butyldimethylsilyloxy)pyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methylamine.

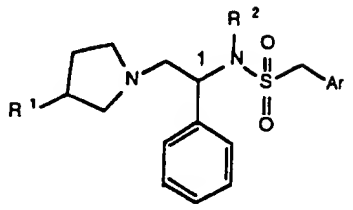
N-[2-(3-(S)-hydroxypyrrolidin-1-yl)-1-(S)-phenylethyl]-N-methyl-(4-trifluoromethoxyphenyl)methanesulfonamide

IR (KBr) 3330, 2960, 1510, 1460, 1335, 1265, 1220, 1200, 1160, 930 cm^{-1}. ^1H NMR δ 7.40-7.25 (m, 5H), 7.20-7.10 (m, 4H), 5.19 (dd, J = 4.4, 11.0 Hz, 1H), 4.35 (d, J = 13.9 Hz, 1H), 4.28 (d, J = 13.6 Hz, 1H), 4.40-4.25 (m, 1H), 3.36-3.15 (m, 2H), 2.85-2.62 (m, 3H), 2.51 (s, 3H), 2.28-2.10 (m, 2H), 1.90-1.55 (m, 2H).

The compounds and their pharmaceutically acceptable salts have excellent activity as opioid κ-receptor agonists. They are useful for the treatment and prevention of pain, asthma, scabies, psoriasis vulgaris or inflammation, especially pain, in mammalian subjects, e. g., human subjects.

Claims

(1) A compound having the chemical formula (I)



(I)

and the pharmaceutically-acceptable salts thereof,

wherein R^1 is hydrogen, hydroxy, C_1-C_6 alkoxy, tri(C_1-C_6 alkyl)silyloxy or acyloxy;

R^2 is C_1-C_6 alkyl; and

Ar is optionally-substituted aryl.

(2) A compound according to claim 1, in which Ar is phenyl, naphthyl, mono-substituted phenyl or mono-substituted naphthyl, wherein the substituent is selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halosubstituted (C_1-C_6) alkyl, halosubstituted (C_1-C_6) alkoxy, C_1-C_6 alkylsulfonyl, nitro, di (C_1-C_6) alkylamino, mono(C_1-C_6) alkylamino monoacylamino, mono (C_1-C_6) alkylsulfonylamino and amino.

(3) A compound according to claim 2, in which R^1 is hydrogen or hydroxy; R^2 is methyl.

(4) A compound according to claim 3, in which Ar is phenyl, naphthyl or substituted phenyl wherein the substituent is 2-chloro, 2-iodo, 2-nitro, 2-amino, 2-dimethylamino, 2-acetylamino, 2-methansulfonylamino, 3-bromo, 3-methoxy, 3-chloro, 4-chloro, 4-fluoro, 4-methyl, 4-nitro, 4-trifluoromethyl, 4-cyano, 4-methoxycarbonyl, 4-methansulfonyl, 4-trifluoromethoxy, 2,3-dichloro, 2,4-dichloro, 2,5-dichloro, 2,6-dichloro, 3,4-dichloro, 3,5-dichloro, 3,4-difluoro, 3,5-difluoro or 2,3,6-trichloro.

(5) A compound according to claim 4, in which

R^1 is hydroxy; and

Ar is substituted phenyl wherein the substituent is 4-methyl, 4-trifluoromethyl, 2,3-dichloro, 2,4-dichloro, 3,4-dichloro or 2,3,6-trichloro.

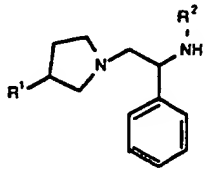
(6) A compound or its pharmaceutically acceptable salt according to any one of claims 1 to 5, in which the carbon atom (C1) is S-configuration or R-configuration.

(7) A pharmaceutical composition for the treatment or prevention of pain in a mammalian subject which is characterized by comprising a compound according to any one of claims 1 to 5 together with a pharmaceutically inert carrier.

(8) A pharmaceutical composition for the treatment or prevention of asthma, scabies, psoriasis vulgaris or inflammation in a mammalian subject, which is characterized by comprising a compound according to any one of claims 1 to 5 together with a pharmaceutically inert carrier.

(9) A method of treating or preventing pain, asthma, scabies, psoriasis vulgaris or inflammation in a mammalian subject, which comprises administering to said subject an effective amount of a compound according to claim 1.

(10) A process for preparing a compound according to claim 1, which comprises reacting a compound of the formula



with $ArCH_2SO_3H$ in the presence of condensing agent or $ArCH_2SO_2Cl$.

INTERNATIONAL SEARCH REPORT

Internat· ·l Application No
PCT/JP 94/00118

A. CLASSIFICATION F SUBJECT MATTER
IPC 5 C07D207/12 C07F7/18 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 374 756 (MERCK PATENT GMBA) 27 June 1990 *Complete document* ---	1-10
A	EP,A,0 483 580 (MERCK PATENT GMBH) 6 May 1992 *Complete document* ---	1-10
A	EP,A,0 223 124 (MERCK) 27 May 1987 *Complete document* -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" documer. published prior to the international filing date but later than tn. priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
2 May 1994	16. 05. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Luyten, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I national application No.
PCT/JP 94/00118

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 9 is directed to a method of treatment of (diagnositc method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...mation on patent family members

Internati... Application No
PCT/JP 94/00118

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0374756	27-06-90	DE-A-	3935371	05-07-90
		AU-A-	4714389	28-06-90
		CA-A-	2006413	23-06-90
		JP-A-	2215769	28-08-90
		US-A-	5232978	03-08-93
EP-A-0483580	06-05-92	DE-A-	4034785	07-05-92
		AU-A-	8553891	07-05-92
		CA-A-	2054648	03-05-92
		JP-A-	4264067	18-09-92
		US-A-	5232978	03-08-93
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